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(54) A PROCESS FOR THE PRODUCTION OF AN ACYLATING AGENT

(71) We, FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of 509 Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to fluorocarbonic acid *tert.*-butyl ester and its production. This new compound is a useful reagent for the preparation of plant protective agents and in peptide synthesis.

Fluorocarbonic acid alkyl esters with primary and secondary alkyl groups are known. They are preparatively used as intermediates for the production of alkyl fluorides. There are two known methods for preparing them. One method starts from the corresponding chlorocarbonic acid alkyl ester which is converted into the fluorocarbonic acid alkyl ester by the exchange of chlorine for fluorine by means of thallium or potassium fluoride. (Houben-Weyl, 4th Edition, volume V/3, page 210). However, this method cannot be used for the production of the new fluorocarbonic acid esters of the present invention, since the corresponding chlorocarbonic acid-*tert.*-butyl ester can only be obtained in poor yields and, moreover, is very unstable (Journal of the American Chem. Soc. *79*, 4684, 1957; Journal of the American Chem. Soc. *70*, 2967, 1948).

The second method of producing fluorocarbonic acid esters consists in acylating alcohols with carbonyl fluoride-chloride or with carbonyl fluoride-bromide. A number of fluorocarbonic acid esters have been prepared by this method (J. Org. Chem. *21*, 1319 [1956]). The production of fluorocarbonic acid-*sec.* butyl ester has been described, *inter alia*, but not that of fluorocarbonic acid-*tert.*-butyl ester.

Fluorocarbonic acid alkyl esters with primary or secondary alkyl groups are mainly used for preparative purposes, in order to produce from them the corresponding alkyl fluorides by thermal decarboxylation. Consequently, the compounds are not very stable to heat. In practice, catalysts such as pyridine and BF_3, are added to the decarboxylation and decomposition temperatures are then reached, which are of the order of 0°C to 25°C in the case of esters of secondary alcohols. Similar decomposition reactions of tertiary carbinols have not been described, as their esters are not known. On account of the known high instability of chlorocarbonic acid-*tert.*-butyl ester and of the facts described above, it was thus to be expected that presumably the fluorocarbonic acid-*tert.*-butyl ester could not be produced for reasons of stability.

The present invention provides a process for the production of fluorocarbonic acid *tert.*-butyl ester which comprises reacting *tert*-butanol with at least the stoichiometrically required amount of carbonyl fluoride-chloride or carbonyl fluoride-bromide, with the elimination of hydrogen chloride or bromide respectively, the reaction being started at substantially −70°C and the elimination of hydrogen chloride or bromide respectively being completed between −20°C and 0°C.

The resultant fluorocarbonic acid-*tert.*-butyl ester, if desired, may be isolated substantially pure, for instance, by distillation at a sump temperature of not more than 0°C. In general, this process is carried out by first placing the *tert.*-butanol in the reaction vessel and then adding the carbonyl fluoride-chloride or carbonyl fluoride-bromide at about −70°C., preferably at about −50°C. It is also possible to operate in the reverse order. If desired, the acylating agent can also be added in an excess of up to about 100%.

[*Price 5s. 0d. (25p)*]

The reaction can also be carried out in the presence of inert solvents, such as fluorotrichloromethane, butane, methyl chloride, methylene chloride. If desired, it is possible to work in *iso*butylene in order to bind the hydrogen chloride or bromide liberated in the reaction. The solution of the reaction components prepared at the aforesaid temperature is then slowly brought, with good stirring, in accordance with the rate at which the hydrogen halide is split off, to temperatures between −20 and −5° C., at most 0° C., and the same temperature is maintained until the reaction is completed, i.e. until the evolution of hydrogen chloride or bromide has subsided.

A connected reflux condenser with a cooler temperature of below −45° C. returns the unreacted carbonyl dihalide to the reaction flask. When the reaction is completed, the mixture is worked up in the usual manner, for example, by fractional distillation. A bath temperature of not more than +20° C. should not be exceeded. The distillation is preferably carried out with the use of an effective cooler at a sump temperature of or below 0° C., preferably at −15 to 0°C. It may sometimes be expedient directly to work up the crude product or the solution of the fluorocarbonic acid-*tert.*-butyl ester obtained by the reaction.

The fluorocarbonic acid-*tert.*-butyl ester which can be obtained by the process according to the invention is a valuable intermediate for the production of plant protective agents and it can also be used as a reagent in the syntheses of peptides in accordance with the co-pending Patent Application No. 58359/67 (Serial No. 1214010) for the introduction of the *tert.*-butoxy-carbonyl groups (for brevity, BOC-radicals). In this co-pending application it is claimed per se. In this connection it has been found that *tert.*-butyloxy-carbonyl derivatives of amino acids can be prepared in a particularly advantageous manner with the aid of *tert.*-butyloxy-carbonyl fluoride. The hitherto unknown BOC-fluoride is substantially more stable than the BOC-chloride. Compared with the sterically hindered BOC-azide, the fluoride reacts under substantially milder conditions. The acylation usually proceeds almost quantitatively within one hour, even at temperatures below 0° C. Thus, the BOC-derivatives of glycine, alanine, leucine, isoleucine, proline, phenylalanine, α-carbobenzoxy-lysine and ω-*p*-nitro-carbobenzoxy-lysine have been obtained in crystallized form and with yields of about 90% by using BOC-fluoride. Serine, threonine, aspartic acid and glutamic acid also smoothly react with the fluoride at 0° C. and also at room temperature and at pH 9.2 to 9.5 within a short time, and the BOC-derivatives can be isolated in yields of about 90%. For example, the BOC-N-methyl-DL-valine is obtained via the BOC-azide in the pH-stat process after 48 hours at pH 10.5 in a yield of 53%, whereas the method via the fluoride yields 75% of crystallized BOC-N-methyl-DL-valine within 2 1/2 hours at pH 9.5.

Also the semi-esters or semi-amides of α-amino-dicarboxylic acids can be acylated with the BOC-fluoride easily and with better yields than are obtained according to known processes, as the reaction can be carried out at pH values at which a noticeable hydrolysis of the carboxylic acid derivatives does not take place.

The conditions for the synthesis and the physical data of some BOC-aminoacids prepared by reaction with the BOC-fluoride and NaOH with pH control are compiled in the annexed Table I.

Moreover, the annexed Table II compares the reaction conditions and yields of the pH-controlled synthesis via the BOC-azide with that via the BOC-fluoride.

As a further advantage, the reagent offers the possibility of protecting histidine by the *tert.*-butyloxy-carbonyl radical also on the imidazole (=im) groups. The *im*-BOC group is labile to alkali and is split off by anhydrous trifluoroacetic acid within 60 minutes. The acylation can be carried out at room temperature, but it is particularly advantageous to work at temperatures about 0° C. with pH control. For example, BOC-aspartic acid-β-benzyl ester did not crystallize when the pH value rose during the reaction to above pH 10 even for a short time.

The reagent is also suitable for the acylation of amino-acid esters. Suitable aminoacid components are racemic and natural as well as synthetic L- and D-amino acids, iminoacids with at least one hydrogen atom on the nitrogen, aminoacids with additional carboxyl groups or amino groups. Besides the aminocarboxylic acids, aminosulphonic acids and aminophosphoric acids can also be acylated with this reagent.

The use of fluorocarbonic acid-*tert.*-butyl ester for introducing the BOC-radical are non-limitatively illustrated by the following Experiments:

(a) BOC-L-aspartic acid

3.3 Grams of aspartic acid were suspended in a mixture of 5 ml of dioxan and 5 ml of H_2O and cooled to −4° C. A total of 6 ml or crude BOC-fluoride (appr. 60%) were then added in 3 portions with vigorous stirring and a pH of 9.5 was maintained by means of an autotitrator. The absorption of alkali was completed after 30 minutes. After a further 60 minutes, the mixture was filtered off from a small amount of precipitate, rinsed with a little water, and the still alkaline solution was extracted with 30 ml of ether. The solution was then cooled to 0° C. and rendered acidic by the addition of solid citric acid. The solution was then extracted with a total of 150 ml *sec.*-butanol in 3 portions and the

extracts were washed three times with 10 ml portions of a saturated NaCl solution and finally twice with 5 ml portions of water. The butanol was then distilled off in a vacuum and the residual oil was dissolved in ethyl acetate, filtered and mixed with petroleum ether. Upon evaporation of the solution, 4.1 g of the compound crystallized and were thoroughly washed with petroleum ether. Yield 71%; m.p. 114 to 116° C.
$[\alpha]_{578}$ −6.2; (for literature cf. Table I).

(b) BOC-L-aspartic acid-β-benzyl ester

4.5 Grams of aspartic acid-β-benzyl ester were suspended in a mixture of 5 ml of dioxan and 5 ml of H_2O and, after cooling to −40° C., reacted with a total of 6 ml of crude BOC-fluoride at pH 8.8, the pH being maintained at 8.8 ± 0.2 by the automatic addition of 4N NaOH. The reaction was completed after one hour. After further stirring for one hour, a small amount of precipitate was filtered off with suction, the filtrate acidified with solid citric acid and the oil separated by extracting three times with 30 ml portions of ethyl acetate. The combined extracts were repeatedly washd with 10 ml portions of H_2O and the ethyl acetate was removed in a vacuum. 6.5 Grams (100%) of the desired product remained behind in crystallized form. After recrystallization from ethyl acetate/petroleum ether, there were obtained 5.55 g (86%) of m.p. 95 to 97° C.; $R_{F\ SBN}$ 0.62; $[\alpha]_{578}$ +7.1 (c = 1; glacial acetic acid).

(c) BOC-L-glutamic acid-γ-benzyl ester

5.4 Grams of glutamic acid-γ-benzyl ester were suspended in 10 ml of a 1:1 mixture of dioxan and water and reacted with a total of 6 ml of crude BOC-fluoride at pH 8.8. The material slowly dissolved. The mixture was suction-filtered after 1 1/2 hours—pH 9.2—and thoroughly washed with water. The residue contained, besides a little unreacted glutamic acid-γ-benzyl ester ($R_{F\ SBA}$ +60), mainly free glutamic acid ($R_{F\ SBA}$ 0.12) formed by hydrolysis of the γ-ester, as well as traces of the desired compound. After extracting the reaction solution with 30 ml of ether, the aqueous phase was acidified with citric acid and extracted with a total of 100 ml of methylene chloride in three portions. The methylene chloride solution was washed several times with 10 ml portions of H_2O and finally concentrated in a vacuum. The desired compound remained as a colorless syrup; $R_{F\ SBN}$ 0.64; yield 6.4 g (83%).

(d) BOC-L-serine

5.7 Grams of serine were suspended in 10 ml of dioxan and, while cooling to −15° C., there were added 10 ml of 4N NaOH followed by 15 ml of crude BOC-fluoride. The mixture was stirred, initially with cooling, at room temperature for 2 hours, a pH of 9.5 being maintained. After a slight turbidity had been filtered off with suction, the filtrate was extracted with 30 ml of ether, acidified with citric acid and, after the addition of sodium chloride, extracted four times with 30 ml portions of ethyl acetate. The combined extracts were repeatedly washed with 10 ml portions of a saturated sodium chloride solution and finally twice with 10 ml portions of water. By distilling off the solvent, there were obtained 9.3 g of a syrupy residue (90%) with $R_{F\ SBN}$ 0.42. The syrup completely crystallized upon standing. The hydrate present melted at 75 to 78° C.; $[\alpha]_{578}^{22}$ −4.3; (c = 1, in glacial acetic acid).

(e) BOC-N-methyl-DL-valine

5.75 Grams of N-methyl-DL-valine were suspended in 10 ml of 50% dioxan, the suspension was cooled to −20° C., and 15 ml of BOC-fluoride were added. The mixture was stirred, initially with cooling, at pH 9.7 and allowed to reach room temperature. After 2.5 hours, a flocculent precipitate was filtered off with suction and the filtrate was first extracted with 30 ml of ether. After acidification with citric acid, the solution was extracted with 120 ml of ether in three portions. The ethereal phases were de-acidified by washing three times with 10 ml portions of water and the ether was distilled off in a vacuum. As residue there remained 10 g of a pale yellow oil (94%) which finally crystallized in petroleum ether. Yield 8.1 g (75%) of m.p. 81 to 83° C.; $R_{F\ SBN}$ 0.62.

All the further derivatives contained in Table I were prepared in an analogous manner under the conditions indicated in the Table.

+) SBN = 85 parts by volume of *sec.*-butanol and 15 parts by volume of 10% ammonia
SBA = 75 parts by volume of *sec.*-butanol, 15 parts by volume of water and 10 parts by volume of 90% formic acid.

TABLE I

Amino acid	pH	Reaction temp. °C.	React. time	Yield	'Lit.	Melting point	'Lit.	α578	(Solv.)	'Lit.
L-alanine	9.5	– 4	2	92	55.5[1])	81– 83	83– 84[1])	– 24.5 (HOAc)	– 22.4[1])	(HOAc)
L-aspartic acid	9.5	– 4	1.5	70	34[2])	114–116	118–119[2])	– 6.2 (Me)	– 6.2[2])	(Me)
L-aspartic acid β-benzyl ester	8.8	– 4	1	86	—	95– 97	—	+ 7.1 (HOAc)	—	
L-asparagine	9.2	– 4	5	79	73[3]) 45[3])	174–176	181–182[3]) 200[3])	– 8.0 (DMF)	– 7.8[3])	(DMF)
L-cystine	9.2	– 4	2	80	67[4])	146–147	145–146[4])	–114.6 (HOAc)	–138 [4])	(Me)
L-glutamic acid	9.5	– 4	1.5	84	58[5]) 75[6])	110–112	110–112[5]) 115[6])	– 15.6 (Me)	–16.1[5])	(Me)
L-glutamic acid γ-benzyl ester	8.8	– 4	2	82		syrupy		—	—	
glycine	9.2	– 4	2	85	56[7]) 77[1])	84– 86	85– 89[1])	—	—	
L-isoleucine	9.4	– 4	1	92	9.6[1])	66– 68	49– 57[1])	+ 2.5 (HOAc)	+ 3[1])	(HOAc)
L-leucine	9.5 9.5	20 – 4	1 1.5	95 93	59[1]) 72[8])	78– 81	74– 80[8])	– 28.2 (HOAc)	– 24.0[1])	(HOAc)
α-carbobenzoxy-L-lysine	9.2	– 4	1	96	93[9])	76– 78	syrupy	– 3.0 (HOAc)		
ε-carbobenzoxy-L-lysine	9.4	– 4	5	90	62[1])		syrupy[1])	—	—	
ε-*p*-nitrocarbobenzoxy-L-lysine	9.2	– 4	4	85	—	103–105	—	– 6.1 (HOAc)	—	
L-methionine	9.4	– 4	1.5	92	40[1])		syrupy	—	—	

TABLE—cont.

Amino acid	pH	Reaction temp. °C.	React. time	Yield	'Lit.	Melting point	'Lit.	α578	(Solv.) 'Lit.
N-methyl-DL-valine	9.7	20	2.5	75	—	82— 84	—	—	—
L-phenylalanine	9.4	— 4	2	89	73[1]) 79[8])	82— 83	79—80[1])	— 4.0 (HOAc)	— 0.8[1]) (HOAc)
L-proline	9.0	— 4	1.5	95	55[1])	132—134	136—157	— 62.5 (HOAc)	— 60[1]) (HOAc)
L-serine	9.5	20	1.5	90	—	75— 78	—	— 4.3 (HOAc)	—
		— 4	1.5	85	—	(hydrate)			
o-tert.-butyl-L-serine	9.2	— 4	1.5	92	—	126—128	—	± 0 (HOAc)	—
L-threonine	9.5	20	1	75[10])		74— 77	76— 80[10])	— 9.5 (HOAc)	— 2.5[10]) (Me)
		— 4	1.5	94					
L-valine	9.2	— 4	2	93	55[1]) 68[8])	72— 73	77— 79[1])	+ 6.0 (HOAc)	— 5.8[1]) (HOAc)

Solv. = solvent.: HOAc = acetic acid; Me = methanol; DMF = dimethyl formamide.

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TABLE II

Amino acids	BOC-Azide (pH-control) pH	Reaction cond. Temp. °C.	time (hrs.)	yield %	BOC-Fluoride (pH-control) pH	Reaction cond. Temp. °C.	(time hrs)	Yield %
L-aspartic acid	10.2	20	26	68	9.5	− 4	1.5	70
L-aspartic acid-benzyl ester	9.8	22		*	8.8	− 4	1	86
L-asparagine	9.9	21	26	72**	9.0	− 4	3.5	79
L-glutamic acid	10.0	19	13	97	9.5	− 4	1.5	84
L-glutamic acid-γ-benzyl ester	9.8	20	—	*	8.8	− 4	2	83
ε-*p*-nitrocarbobenzoxy-L-lysine	9.9	22	12	96***	9.2	20	4	85
L-phenylalanine	10.1	20	13.5	91	9.4	− 4	2	89
L-serine	9.3	20	29	85	9.5	− 4	1.5	90
L-threonine	9.5	22	30	88	9.5	− 4	1.5	94
N-methyl-DL-valine	10.5	25	48	53	9.7	20	2.5	75

* Under these conditions the ω-benzyl ester is substantially hydrolyzed.

** Ammonia escapes from the reaction vessel.

*** compound did not crystallize.

Furthermore, it is possible to use for the introduction of protective groups in peptide syntheses, instead of fluorocarbonic acid-*tert.*-butyl ester, the p-methoxy-benzyloxy-carbonyl fluoride (=MZ: n_D^{20} 1.4985; carbonyl band in the infrared spectrum at 1820 cm^{-1}) as well as the furfuryloxycarbonyl fluoride (= FOC: n_D^{20} = 1.4381; carbonyl band in the infrared spectrum at 1820 cm^{-1}). The reactions are carried out with Mz at −20 to +20°C., with FOC at −20 to +10°C., in the presence of acid-binding agents.

The process of the invention is illustrated by the following non-limiting Example.

EXAMPLE

370 Grams of *tert.*-butanol are placed in a three-necked flask which is fitted with a stirrer, a thermometer and a reflux condenser kept at −60° C., and 595 g of carbonyl fluoride-chloride are condensed on at a bath temperature of about −70° C. Part of the butanol dissolves already during this operation. The contents of the flask are then heated. At a sump temperature of −40° C. a marked reflux (cooler temperature below −45° C.) and a slight evolution of hydrogen chloride set in. After 1 1/2 hours, the reaction temperature is allowed to rise gradually in the course of 3 hours to a temperature of −10° C. The excess carbonyl fluoride-chloride is then removed via a connected descending low temperature condenser by raising the temperature of the reflux condenser. The evolution of hydrogen chloride becomes noticeably stronger at about −30° C. and is quite rapid at −20° C. At this temperature a completely clear water-white solution is also formed. The reaction solution is further stirred at −10° C. until the evolution of hydrogen chloride has subsided. Duration about 5 to 6 hours. This crude solution can be used for further reactions after a short degassing by application of a weak vacuum of about 200 mm Hg. Its content of fluorocarbonic acid-*tert.*-butyl ester amounts to about 60%, the remainder is mainly *tert.*-butanol. The pure fluorocarbonic acid-*tert.*-butyl ester is obtained by distillation. B.p. −8° C. to −7° C./1.9 mm Hg; n_D^{10} 1.3591. The carbonyl band in the infrared spectrum is at 1830 cm^{-1}.

Analysis: $C_5H_9FO_2$ (molecular weight 120.13)
Calc.: C 50.0% H 7.5% O 26.7% F 15.9%
Found: C 50.4% H 8.0% O 26.7% F 15.1%

Virtually the same results are obtained when the reaction is carried out in the presence of trichloro-fluoro-methane as solvent or in the presence of isobutylene as hydrogen chloride acceptor.

WHAT WE CLAIM IS:—

1. A process for the production of fluorocarbonic acid *tert.*-butyl ester which comprises reacting *tert.*-butanol with at least the stoichiometrically required amount of carbonyl fluoride-chloride or carbonyl fluoride-bromide, with the elimination of hydrogen chloride or bromide respectively, the reaction being started at substantially −70°C and the elimination of hydrogen chloride or bromide respectively being completed between −20°C and 0°C.

2. The process of claim 1 wherein the fluorocarbonic acid *tert.*-butyl ester is subsequently obtained substantially pure.

3. The process of claim 2 wherein the fluorocarbonic acid *tert.*-butyl ester is isolated by distillation at a sump temperature of from −15°C to 0°C.

4. The process of claim 1 wherein the fluorocarbonic acid *tert.*-butyl ester is isolated in the form of its solution.

5. The process of any one of the preceding claims wherein the reaction is carried out in the presence of at least one inert solvent.

6. The process of any one of the preceding claims wherein the reaction is carried out in the presence of *iso*butylene.

7. The process of any one of the preceding claims wherein an excess of up to about 100% of the carbonyl halide is used.

8. The process of any one of the preceding claims wherein the carbonyl halide is added at about −50°C.

9. The process of any preceding claim, substantially as hereinbefore described in the Example.

10. Fluorocarbonic acid *tert.*-butyl ester ever prepared by the method of any one of claims 1 to 9.

11. A process for the manufacture of plant protective agents comprising the use of the compound of claim 10 as an intermediate.

12. Plant protective agents whenever made by the process of claim 11.

13. A process for the preparation of BOC-derivatives of amino acids, amino acid esters, or peptides comprising the use of the compound of claim 10 as a reagent.

14. The process of claim 13 substantially as hereinbefore described in any of Experiments (a) to (c) or in Table I or II.

15. BOC-derivatives of amino acids, amino acid esters, and peptides whenever prepared by the method of claim 13 or 14.

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